UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT:

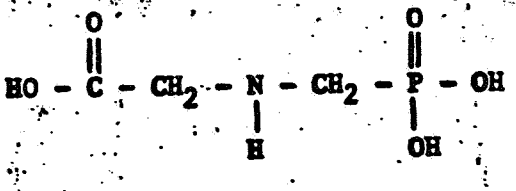
DATE: September 13, 1974

FROM:

TO: Coordination Branch
Registration Division (WH-567)

Registration No.:	524-EXP
Product name:	Roundup
Registrant:	Monsanto
Action requested:	Experimental permit
Related petitions:	4G1444, 5G1523
Existing temporary tolerance under	4G1444: In or on corn grain including popcorn, fresh corn including sweet corn (kernels plus cob with husk removed), soybeans, wheat grain and wheat forage and straw at 0.1 ppm.
Use:	Herbicide
Identified as:	Technical CP 67573 Glyphosate Water-based formulation 70139 Mon 2139

Chemical Identity:



Chemical and Physical Properties

Form: White crystalline solid
M.P.: 200° C
Solubility: Soluble in water 1.0% at 25° C
Insoluble in ethanol, acetone, benzene

Stability: Stable to melting point

Bulk Density: 45 lb/gal

Assay: Technical material 98%

Formulation:

Active Ingredient:	%
N-phosphonomethyl glycine, isopropylamine salt	41.0
Inert Ingredients:	
[redacted]	[redacted]
	100.0

Summary Toxicological Evaluation

Acute Studies

Species	Route	Formulation	LD_{50} or Dose mg/kg	Observations
Rat (M&F)	Oral	Technical	4320 (3930-4750)	Lethargy, diarrhea, weakness collapse. Hemorrhagic lungs and liver. GI inflammation.
Rabbit (M&F)	Oral	Technical	3899 (2836-5092)	Hypoactivity in 1 hr to 10 days. Death in 3-11 days.
Rat (M&F)	Oral	~~36%~~ 41%	4900 (4400-5400)	Same as for technical.
Rat (M&F)	Oral	41%	4040 (3660-4460)	Same as for technical
Rabbit (M&F)	Dermal	Technical	> 7940	No signs of systemic toxicity.

Species	Route	Formulation	LD_{50} or Dose mg/kg	Observations
Rabbit (M&F)	Dermal	~~30%~~ 41%	> 7940	Hypoactivity
Rat (M&F)	Inhalation (4 hrs)	41%	> 12.2 mg/l	No signs of systemic toxicity
Rabbit (M&F)	Skin irritation (24 hr exposure)	Technical	0.5 gm	No irritating score 0/8
Rabbit (M&F)	Skin irritation (24 hr exposure)	~~30%~~ 41%	0.5 ml	Mild irritant, score 2.3/8
Rabbit	Eye irritation (24 hr exposure)	Technical	100 mg	Slight irritation max. score 12.6/110 in one hour
Rabbit	Eye irritation (24 hr exposure)	~~30%~~ 41%	0.1 ml	Severe irritant, max. score 64.3/110 in 7 days. Corneal opacity and ulceration
Rabbit	Eye irritation (15 min. exposure)	~~30%~~ 41%	0.1 ml	Mild irritation, max. score 16/110 in 1 hr. Normal in 7 days.
	(30 min. exposure)	~~30%~~ 41%	0.1 ml	Mild irritation, max. score 15.3/110 in 1 hr. Normal in 7 days.
	(15 min. exposure)	5%	0.1 ml	Slight irritation, max. score 12/110 in 1 hr. normal in 7 days.
	(30 min. exposure)	5%	0.1 ml	Slight irritation, max. score 12.6/110 in 1 hr. Normal in 7 days.
	(24 hr. exposure)	5%		Slight irritation, max. score 11.3/110 in 1 hr. Normal in 7 days.

Species	Route	Formulation	LD_{50} or Dose mg/kg	Observations
Rat (M&F)	Oral		8300 (7300-9460)	Same as for technical
Rabbit (M&F)	Skin irritation	Moistened with water	0.5 gm	Score 0.0
Rabbit (M&F)	Eye irritation		100 mg	Slight irritant max. score 10/110 in 1 hr.

Subacute Studies

Species	Study	Exposure	Formulation	Observations
Rabbit	Dermal Intact and Abraded	Daily 15	Water-based 1.64% (use conc.)	Phonation Red well defined erythema, moderate edema and escharosis. Pustules and hemorrhaging. No deaths Increase in leukocyte count and neutrophils with decreased % lymphocytes
			8.2%(5X use conc)	Same gross and hematologic findings as above with 5/20 deaths.
Human (50)	Repeated Patch	15	1:9 dilution of the 30% water-based	This material is not a primary irritant, fatiguing or sensitizing agent.
Dog	Feeding	90	Technical at 0, 200, 600 and 2000 ppm	No effect level is greater than 2000 ppm
Rat	Feeding	90	Technical at 0, 200, 600 and 2000 ppm	No effect level is greater than 2000 ppm

Chronic Studies

Species	Study	Exposure	Formulation	Observation
Mice	Carcinogenic feeding	18 month	Technical at 0, 100 and 300 ppm	Not tumorigenic nor carcinogenic at 300 ppm
Rats	Reproduction feeding		Technical at 0, 30, 100 and 300 ppm	No effect level is greater than 300 ppm

Special Studies

Mutagenic - not mutagenic at 10 mg/kg (highest level tested)

Teratogenic study - not teratogenic at 30 mg/kg (highest level tested)

Metabolism - Rabbit, single oral doses of C^{14} phosphonemethyl in doses of 5.7 to 8.8 mg/kg.

Results: More than 90% C^{14} activity cleared within 5 days, with 80% in feces, 7-11% in the urine and less than 1% expired as CO_2. Tissue concentration of carboxyl moiety was liver ≥ kidney ≥ spleen > heart, muscle and gonads.

Metabolism - Rats, single oral dose of methylene carboxyl, or alpha carbon labeled C^{14} phosphonomethyl glycine at 6.7 mg/kg

Results: Within 48 hours male rats cleared 94-98% of the dose as compared to 82-84% for female rats. By 120 hours, 99% of the dose was cleared by both male and female. The label distribution in the feces is carboxyl > alpha carbon > methylene. Males excreted 15% of the dose in the urine with the remainder recovered in feces. Females excreted 35-40% of the dose in the urine with remainder recovered in feces.

Metabolism - Rats, single oral dose of C^{14} aminomethyl phosphonic acid at 6.7 mg/kg.

Results: Within 120 hours 74% of the dose appeared in the feces, 20% in urine and less than 0.1% expired CO_2. More than 50% of the dose was excreted in the feces within 24 hours.

Metabolism - Rat, C^{14} labeled N-phophonomethyl glycine was administered by gastrointubation or intraperitoneal injection at 6.7 mg/kg.

Results: N-phosphonomethyl C^{14} glycine is excreted when administered by either route, in the urine and feces as the parent compound.

Metabolism - Rat dietary levels of phosphonomethyl C^{14} glycine were fed at 1.0, 10 and 100 ppm for 14 days followed by a 10 day withdrawal period.

Results: Excretion in both urine and feces reached a plateau level by the sixth day. Most tissue levels plateaued within 10 days or less. The ingested test material was excreted from the body by apparent first order processes so that the amount excreted was directly proportional to the intake. Upon withdrawal, excretion dropped sharply but plateaued temporarily after four days. This excretory plateau during the withdrawal period was due to the excretion of the mobilized tissue residues which were cleared by the kidney or secreted into the intestine with the bile. The cumulative effect was not localized in a single tissue or organ system and was clearly reversibly bound.

Conclusion:

The toxicity data provided in connection with the prior petitions demonstrate the levels of adverse effects which can be produced by this chemical. The percautionary labeling provided for the product under evaluation clearly states the use hazards and their prevention.

Recommendation:

The experimental permit for the applied use be granted.

Robert D. Coberly, Biologist
Toxicology Branch
Registration Division (WH-567)

cc: Division File
Branch Reading File

RDCoberly:ssr:9/13/74